

Swiss Federal Institute of Intellectual Property
Einsteinstrasse 2
CH 3003 Bern
Telephon: +41 31 325 25 25
Fax: +41 325 25 26
Mail : info@ipi.ch
Homepage: <http://www.ige.ch>

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(21) International Application Number: PCT/US91/01898 (22) International Filing Date: 26 March 1991 (26.03.91) (30) Priority data: 514,021 27 April 1990 (27.04.90) US 598,383 16 October 1990 (16.10.90) US (71) Applicant: MOLECULAR RX., INC. [US/US]; 310 25th Avenue North, Suite 350, Nashville, TN 37203 (US). (72) Inventors: KLINE, Ellis, L. ; 203 N. Elm, Pendleton, NC 29670 (US). MCMICHAEL, John ; P.O. Box 127, Delanson, NY 12053 (US). (74) Agents: WEGNER, Harold, C. et al.; Wegner, Cantor, Mueller & Player, 1233 20th Street, N.W., Suite 300, P.O. Box 18218, Washington, DC 20036-8218 (US).		(81) Designated States: AT (European patent), BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), SE (European patent). Published <i>With international search report.</i>
(54) Title: METHOD AND COMPOSITION FOR TREATMENT OF CENTRAL NERVOUS SYSTEMS DISEASE STATES ASSOCIATED WITH ABNORMAL AMYLOID BETA PROTEIN (57) Abstract A method and composition are provided for alleviation of disease states associated with the abnormal accumulation and/or molecular organization of amyloid beta protein, such as manifested in Alzheimer's disease and other CNS amyloid disorders. The invention comprises the administration of a low level of amyloid beta protein, or a derivative thereof, which slows or reverses neuronal loss or function.		

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METHOD AND COMPOSITION FOR TREATMENT OF CENTRAL NERVOUS
SYSTEMS DISEASE STATES ASSOCIATED WITH ABNORMAL
AMYLOID BETA PROTEIN

SUMMARY OF THE INVENTION

5 In accordance with a first aspect of the invention there is provided a method for alleviating the symptoms of disease states associated with abnormal accumulation of and/or molecular organization of amyloid beta protein, neuritic plaques or amyloid plaques associated with central nervous
10 system and histopathologically related disorders, which comprises administration to the disease patient of an effective dose of a substance which is amyloid beta protein or an active fraction thereof. In a preferred embodiment, the administration of amyloid beta protein provides an amount
15 of no more than about 10^{-2} mg. per dosage unit. In one embodiment, the amyloid beta protein is the entire amyloid beta protein. In an alternate embodiment, the amyloid beta protein is a fraction of amyloid beta protein. In a preferred embodiment, the amount of either the amyloid beta
20 protein or fraction thereof is about 10^{-4} mg. Preferably, the daily adult dosage does not exceed about 10^{-2} mg. per adult bodyweight, and still more preferably does not exceed about 10^{-4} mg.

In a second aspect of the invention there is provided a
25 pharmaceutical composition comprising a vehicle for a single administration of amyloid beta protein or fraction thereof which comprises an amount of up to about 10^{-2} mg. amyloid beta protein or fraction thereof and pharmaceutically inert ingredients. The total amount of the pharmaceutical and the
30 vehicle per dosage unit should be at least about 0.05 to 2 cc total aqueous dosage for an aqueous form or at least about 100 mg. for a solid form so that the total amount is sufficient for convenient administration. In a preferred aspect the pharmaceutical composition has an amount of from
35 about 10^{-8} to about 10^{-2} mg. amyloid beta protein or fraction

thereof. In one embodiment, the vehicle is an aqueous solution that is contained within an inert container, for example, the solution may be an injectable form. In an alternate embodiment, the pharmaceutical composition has a vehicle which is solid, such as a sublingual tablet. In another variation, the composition is in the form of a suppository.

DETAILED DESCRIPTION OF THE INVENTION

Cellular skeletal systems have three distinct ultrastructures made of fibrous macromolecules: microtubules, intermediate filaments and microfilaments, all of which are associated with the central nervous system (CNS) and other histopathological disorders. The neuronal intermediate filaments, defined as neurofilaments (containing amyloid beta protein constructs), are distinct from other intermediate filaments found in the cells of the central nervous system. R.D. Goldman, A. Milstead, J.A. Schloss and M.J. Yerna, Annu. Rev. Physiol. 41 p. 703-722 (1979); R.J. Lasak, Neurosci. Res. Program Bull. 19 p. 7-32 (1981); R.J. Lasek and M.L. Shelanski, Neurosci. Res. Program Bull. 19 p. 3-153 (1981); C.A. Marett, ed., Neurofilaments (1983); M.L. Shelanski and R.K.H. Liem, J. Neurochem. 33 p.5-13 (1979). Neurofilaments are composed of three proteins with molecular weights of 200,000, 150,000 and 70,000 daltons. B.H. Toh, L.J. Gibbs, Jr., D.C. Gajdusek, J. Goudsmit and D. Dahl, Proc. Natl. Acad. Sci. USA. An additional 62,000 dalton protein is also affiliated with the above mentioned proteins. These above proteins are associated with slow axoplasmic transport. P.N. Hoffman and R.J. Lasek, J. Cell Biology 66 p. 351-366 (1975).

Alzheimer's disease, and other amyloid associated maladies such as senile dementia, Down's syndrome, Pick's disease, progressive supranuclear palsy, multiple sclerosis and

others, are characterized by the presence of one or more fused fibrils of repetitive amyloid beta proteins or other similar amyloid residues such as paired helical filaments, neurofibrillary tangles, neuritic plaques, amyloid plaques and cerebrovascular amyloidosis. B.H. Anderson, D. Breinberg and M.J. Downes, Nature 298 p. 84-86 (1982). These paired helical filaments are indistinguishable immunologically and chemically from normal neurofilaments and share many of the same proteinaceous epitopes. B.H. Anderson, D. Breinberg and M.J. Downes, Nature 298 p. 84-86 (1982); B.H. Toh, L.J. Gibbs, D.C. Gajdusek, J. Goudsmit and D. Dahl, Proc. Natl. Acad. Sci. USA; K. Iqbal, I. Grundke-Iqbal, H. M. Wisnieski and R.D Terry, Brain Res. 142 p. 321-332 (1975). It has been suggested that these interfere with axonal transport. P.N. Hoffman and R.J. Lasek, J. Cell Biol. 66 p. 351-366 (1975); J.W. Griffin, P.N. Hoffman, A.W. Clark, P.T. Carroll and D.L. Price, Science 202 p. 633-665 (1978).

Using the cDNA clone of the gene encoding amyloid beta protein as a genetic probe, it was shown that the gene is located on chromosome twenty-one and is expressed in many tissues of the body. D. Goldjaber, M.I. Lerman, O.W. McBridge, U. Suffiotti, and D.C. Gaidusak, Science 235 P. 77-780 (1987); R.E. Tanzi, J.F. Gusella, P.C. Watkins, G.A.P. Bruns, P. St.George, M.L. Vankeuren, D. Patterson, S. Pagan, D.M. Kurnit and R.L. Neve, Science 235 p. 880-884 (1987). Quantitation of amyloid beta protein expression, as seen by its mRNA levels using the cDNA probe, has revealed that its level of expression in brain tissue of Alzheimer's was not above that seen for other tissues outside the central nervous system. This was of interest to researchers when noting that amyloid plaque formation only occurs in the brain. R.E. Tanzi, J.F. Gusella, P.C. Watkins, G.A.P. Bruns, P.

St.George, M.L. Vankeuren, D. Patterson, S. Pagan, D.M. Kurnit and R.L. Neve, Science 235 p. 880-884 (1987).

Amyloid beta protein is obtained through conventional means known in the art and has been characterized by various scientists. A.S. Cohen and E. Calkins, Nature 183 p. 1202 (1959), A.S. Cohen and E. Calkins, J. Cell Biology 21 p. 481 (1964); A.S. Cohen, E. Calkins and C. Levens, Am. J. Pathol. 35 p. 979 (1959). More recent work is manifested by D. Caspi, M.C. Baltz and M.K. Pepys, Mol. Biol. Med. 3 pp. 387-407 (1986); and D. Caspi, M.C. Baltz and M.K. Pepys, Mol. Biol. Med. 3 pp. 409-424 (1986). Amyloid beta protein exists in various structural forms. The amyloid beta protein that has been experimentally used and as referred to herein in terms of any specific embodiments constitutes a mixture of such forms. It is to be understood that within the scope of the present invention it is contemplated that any of the various forms of amyloid beta protein may be used.

Amyloid beta protein from the brain has been cDNA cloned and shown to contain a unique twenty amino acid NH₂-terminal sequence. Glenner, G.G. and Wong, W., Biochem. Biophys. Res. Comm. 122 No. 3, pp. 1131-35 (1984) (herein: Glenner & Wong); D. Caspi, M.C. Baltz and M.K. Pepys, Mol. Biol. Med. 3 pp. 409-424 (1986); Goldgaber, D., Lerman, M.I., McBride, O.W., Saffiotti, U., and Gaidusak, D.C., Science 235, pp. 777-80 (1987). It is to be understood that any active fraction of beta amyloid protein that may be determined to possess the pharmaceutical efficacy expressed herein is specifically contemplated in lieu of the various structural conformations. There are various well known fractions of beta amyloid protein that are set forth in the literature including the previously discussed reference of Glenner & Wong. Subsequent to the present invention herein there has been a recognition by others that such fractions are useful in the treatment of

CNS disorders such as Alzheimer's disease, including an identification of various fractions and equivalents. See Bruce A. Yankner, Lawrence K. Duffy and Daniel A. Kirschner, Science 250, pp. 279-282, 280 (1990) ("Yankner, Duffy & Kirschner").

It has been observed that a buildup of abnormally organized amyloid beta protein in brain tissue is manifested in Alzheimer's disease. See Dennis J. Selkoe and Carmela R. Abraham, "Isolation of Paired Helical Filaments and Amyloid
10 Fibers from Human Brain", 134 Methods in Immunology 388-404 (1986). The fact that there is an accumulation of beta amyloid protein in the brain in Alzheimer patients has been demonstrated by post mortem analysis of brain tissue that
15 manifest a concentration of amyloid beta protein as part of an accumulation of parallel filaments or neural fibrillary tangles in the brain that appear characteristic of Alzheimer victims, along with neuritic plaque and cerebral vasculatory amyloidosis.

The presence of amyloid beta protein in fibrils and plaques
20 in Alzheimer's disease, as well as other CNS disorders, has been suggested to be a result of a degradation product of the normal neurofilaments, D. Goldjaber, M.I. Lerman, O.W. McBride, U. Suffiotti and D.C. Gaidusak, Science 235 p. 77-780 (1987); R.E. Tanzi, J.F. Gusella, P.C. Watkins, G.A.P. Bruns, P. St.George, M.L. Vankeuren, D. Patterson, S. Pagan,
25 D.M. Kurnit and R.L. Neve, Science 235 p. 880-884 (1987); M. Baudry, B.R. Dubrin, L. Beasley, M. Leon and G. Lynch, Neurobiol. Aging 7 p. 255-260 (1986); G.G. Glenner, Arch. Path. Lab. Med. 107 p. 218-282 (1983); or possibly due to
30 improper metabolism of byproducts. Further breakdown products of amyloid beta proteins from neurofilaments have also been observed in amyloid plaques, along meningeal vascular walls, and intracortical blood vessels. S.

Bahmanyar, E.J. Williams, F.B. Johnson, S. Young and D.C. Gaidusak, J. Comp. Path. 95 p. 1-5 (1985); M.E. Bruce and H. Fraser, Neuropathol. Appl. Neurobiol 1 p. 189-207 (1981); M.E. Bruce and H. Fraser, Neuropathol. Appl. Neurobiol. 7 p. 289-298 (1981); G.G. Glenner and W. Wong, J. Quaranta and G.G. Glenner, Pro. Nat. Acad. Sci. 82 p. 8729 (1985); D.J. Selkoe, C.R. Abraham, M.B. Podlisky and L.K. Duffy, J. Neurochem. 46 p. 1820 (1986).

During the mid-1960's, Solomon & Moos speculated that there is a close integration between immunological function, the central nervous system, psychophysiological factors (emotions), and disease, both physical and mental. G.F. Solomon and R.H. Moos, Arch. Gen. Psychiatry 11 p. 657-674 (1964). The integration of these systems was initially suggested through observing the presence of abnormal immunoglobulins in schizophrenic patients. G.F. Solomon and R.H. Moos, Arch. Gen. Psychiatry 11 p. 657-674 (1964); J.G. Knight, Lancet 82 p. 1073-1076 (1982); W.J. Fessel and M. Hirata-Hibi, Arch. Gen. Psychiatry 9 p. 601-613. These immune aberrations (termed autoantibodies), which seemed to target certain body cellular structures, G.F. Solomon, Psychoneuroimmunology p. 259-278 (1985); G.F. Solomon and R.H. Moos, Psychosom. Mod. 27 p. 135-149 (1981), supported the concept that there is a close communication between the CNS and the immune system. For instance, met-enkephalin is a neurotransmitter for the CNS system and is a product of activated T-helper cells. G. Zurawaki, M. Benedik, D.J. Kamb, J.S. Abrams, S.M. Zurawaki and F.O. Lee, Science 232 p. 772-775 (1986).

The appearance of autoantibodies specific to the CNS neurofilaments in patients with Alzheimer's and other CNS disorders suggests that the body's immune system may play a role in the disease process. S. Bahmanyar, R.K.H. Liem, J.W.

Griffin and D.C. Gajdusek, J. Neuropathol. Exp. Neurol. 53 p. 85-90 (1984); S. Bahmanyar, M.C. Moreau-Dubois, P. Brown, F. Catala and D.C. Gajdusek, J. Neuroimmunol. 5 p. 191-196 (1983); T.S. Elizan, J. Casals and M.D. Yahr, J. Neurol. Sci. 59 p. 341-347 (1983). The autoantibodies against normal CNS neurofilaments react with the paired helical filaments in neurofibrillary tangles of Alzheimer's disease. D. Dahl and A. Bignami, Exp. Neurol. 58 p. 74-80 (1978); M.E. Bruce, J. Neuropathol. Exp. Neurol. 37 p. 595, abstract (1978).

Animal models for these CNS disorders which are induced with aluminum chloride or β,β' -iminodipropionitrite (IDPN) to form paired helical filaments in neurofibrillary tangles, also react with antibodies directed against CNS neurofilaments. J.W. Griffen, P.N. Hoffman, A.W. Clark P.T. Carroll and D.L. Price, Science 202 p. 633-665 (1978).

Control of such autoimmune reactions theoretically could lead to the alleviation of symptoms manifested by such reactions. Over the past two decades, a body of clinical literature has accumulated relating to the treatment of autoimmune disease (or, more appropriately, diseases reflecting immune dysfunction) using a technique called provocative-neutralization therapy. Miller, Annals of Allergy 38 p. 185-191 (1977); Miller, Trans. Am. Soc. Opth. & Otolar. Allergy 14 p. 159-168 (1974); Miller, Clinical Medicine 81 p. 16-19 (1974). In short, this method, which is commonly employed for allergy therapy, involves subcutaneous or sublingual introduction of an antigen known, or suspected, to provoke symptoms reflective of immune dysregulation. By serial titration of the provoking material, a concentration of that agent can often be determined which will neutralize those symptoms induced by the same substance at a different concentration. This then is a prime example of a dose-dependent phenomenon in which

one dose induces a positive reaction while another dose of the same agent induces a negative response.

Although it is thought that neutralization occurs as a consequence of reestablishing homeostatic functional levels of T8 suppressor cells, it is quite possible that the same antigen used at a neutralizing concentration to reverse immune dysregulation could also, or instead, trigger endocrine and/or neuronal control mechanisms to reverse symptoms. Because of the intimate association between the three control systems (endocrine, immune, nervous) and proven communication pathways between and among the cells comprising these respective systems, a single active molecule, such as amyloid beta protein in the Alzheimer's victim, and related CNS disorders, could reverse symptoms via any or all of these routes.

In accordance with the invention, there is provided a method to stimulate the appropriate metabolic regulatory systems (immune, CNS or endocrine) which retard the progress of the symptoms of Alzheimer's and in theory should be applicable to related disease states. Observations by scientists have now indicated that the apparent elevated amyloid beta protein concentration in Alzheimer's may not be due to an increase in genomic expression, but possibly an activation of a mechanism that induces the reorganization of amyloid moieties from normal neurofilaments into paired helical filaments resulting in neurofibrillary tangles, neuritic plaques or amyloid plaques. D. Goldjaber, M.I. Lerman, O.W. McBride, U. Suffiotti and D.C. Gaidusak, Science 235 p. 77-780 (1987); R.E. Tanzi, J.F. Gusella, P.C. Watkins, G.A.P. Bruns, P. St.George, M.L. Vankeuren, D. Patterson, S. Pagan, D.M. Kurnit and R.L. Neve, Science 235 p. 880-884 (1987); M. Baudry, B.R. Dubrin, L. Beasley, M. Leon and G. Lynch, Neurobiol. Aging 7 p. 255-260 (1986);

G.G. Glenner, Arch. Path. Lab. Med. 107 p. 218-282 (1983).
The mechanisms of the present invention may result in
triggering control processes that correct the rearrangement
of neurofilaments, alter abnormal amyloid beta protein
formation, and/or allow for clearing of the axonal transport
interfering molecular structures.

The alleviation of Alzheimer's disease symptoms observed
following parenterally administered amyloid beta protein as
described herein likely reflects stimulation of appropriate
metabolic regulatory systems in the Alzheimer's disease
patients such that accumulation and/or formation of the
paired helical filaments in neurofibrillary tangle, neuritic
plaque and/or amyloid plaque developments are significantly
altered or slowed and accumulated proteins are eliminated.
This reprogramming to establish proper homeostasis would
allow more efficient transmission of nerve impulses which
would result in clinical improvement of treated Alzheimer's
patients.

Results from early clinical work using parenteral
administration of amyloid beta protein or a derivation
thereof offers hope for the successful treatment of
Alzheimer's disease as well as other disorders associated
with amyloidosis of the central nervous system. Whether the
action of the amyloid beta protein in relieving symptoms of
Alzheimer's disease is due to the regulation of one or more
subpopulations of T-cells, or by some other mechanism, is not
known. It is also not known if a subunit of the natural, or
possibly a modified amyloid beta protein, can also act to
alleviate Alzheimer's disease symptoms, or if a structurally
similar molecule from another source can prove effectual.
It is anticipated that similar or equivalent variations would
be employed by those familiar with the art.

Typically, a pharmaceutical dosage unit of the present invention for the delivery of amyloid beta protein in a low concentration comprises a liquid or solid carrier and an effective amount of amyloid beta protein. The aforesaid effective amount is preferably from about 10^{-8} to about 10^{-2} mg., and still more preferably about 10^{-4} mg., amyloid beta protein in said dosage unit in association with pharmaceutically acceptable excipients. The dosage unit as used herein refers to the amount of the amyloid beta protein that is administered at one time to the patient. It is to be understood that this dosage unit may be delivered several times per day so that the daily dosage may be in multiples of up to five times the dosage unit. The same order of magnitude of daily dosage is therefore still retained for the effective amount as for the dosage unit. The upper level of the daily dosage should not exceed about 10^{-2} mg. per adult.

The amyloid beta protein is administered through standard methods, including sublingual, subcutaneous and transdermal routes, and in dosage units that are either liquid or solid.

One explanation for the mode of action of this invention may be that the amount of this protein administered is sufficient to trigger a negative feedback mechanism to the body such that production of additional amyloid beta protein, possibly through breakdown of normal neurofilaments, is inhibited. Under this theory, the low level of amyloid beta protein, or a derivative thereof, gives a signal to the body to correct the abnormal synthesis/degradation process. The body sensors are then adjusted to normal metabolic control of amyloid beta protein processing that allows the proper balance to reestablish itself, alleviating the abnormal processing. The immune system, as well as the endocrine and CNS control systems, could play an integral regulatory role

in response to the low dose therapy, with the amyloid protein functioning through mechanisms that not only correct the molecular organization of the amyloid beta protein moieties, but clear the interfering amyloid molecular constructs.

5 In a preferred embodiment, the present invention provides administration of amyloid beta protein or a derivative thereof. The amyloid beta protein may be provided either as part of a liquid solution or in a solid powder matrix, and may be administered with conventional excipients to permit
10 ease of administration and accurate dosage delivery.

EXAMPLE I

15 A 67 year old white male with a history of Alzheimer's disease for four years prior to initiating therapy presented with an inability to answer questions, to place names with faces, and to complete his sentences. His wife noted a consistent downhill progression of his condition on a monthly basis. His initial score on the objective test was 5 of a possible 30. After five months of therapy by administering
20 four times per day the dosage unit this patient scored a 12½, was reading roads signs while travelling, and was communicating with family members. Also, the patient appeared to be more relaxed and better able to respond to his wife's efforts to assist him.

EXAMPLE II

25 An 81 year old white male presented who was unable to dress himself, had a flat affect, was poorly communicative, and scored 10½ on the objective test. After three months by administering four times per day the dosage unit of Example I, he scored 17 points, was more animated in speech, could
30 dress himself most days, and was more confident in physical actions.

EXAMPLE III

When initiating this treatment, this patient was a 62 year old white female suffering from a fulminating form of Alzheimer's that had seen her go from being director of nursing in a chronic care establishment to, within one year, requiring constant care, unable to communicate, did not appear to recognize anyone, and scored a 1.5 on the objective test. After three months of administering four times per day the dosage unit of Example I, the patient's husband reported that warmth had returned to the patient's hands, no deterioration of any type was evident although prior to therapy he could note weekly declines, communication remained difficult but improved, she showed increased alertness, and she was not only able to recognize individuals consistently, but also was able at times to participate in conversations, and her test score rose to 7.75.

WHAT IS CLAIMED IS:

1. A method for alleviating the symptoms of disease states associated with abnormal accumulation of and/or molecular organization of amyloid beta protein, neuritic plaques or amyloid plaques associated with central nervous system and histopathologically related disorders, which comprises administration to the disease patient of an effective dose of substance which is amyloid beta protein or an active fraction thereof.

2. A method of claim 1 wherein administration of amyloid beta protein or fraction thereof provides an amount of no more than about 10^{-2} mg. per dosage unit.

3. A method of claim 2 wherein amyloid beta protein is in the form of the amyloid beta protein itself.

4. A method of claim 2 wherein amyloid beta protein is a fraction of amyloid beta protein.

5. A method of claim 2 wherein said amount is about 10^{-4} mg.

6. A pharmaceutical composition comprising a vehicle for a single administration of amyloid beta protein or fraction thereof which comprises an amount of up to about 10^{-2} mg. amyloid beta protein or fraction thereof and pharmaceutically inert ingredients.

7. A pharmaceutical composition of claim 6 wherein said amount is from about 10^{-8} to about 10^{-2} mg. amyloid beta protein or fraction thereof.

8. A pharmaceutical composition of claim 7 wherein said vehicle is an aqueous solution that is contained within an inert container.

9. A pharmaceutical composition of claim 7 wherein said vehicle is a solid.

10. A pharmaceutical composition of claim 9 in the form of a sublingual tablet.

11. A pharmaceutical composition of claim 9 in the form of a suppository.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US91/01898

I. CLASSIFICATION OF SUBJECT MATTER in several classification symbols apply, indicate all *

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC (5): A01N 37/18; A61K 37/00

U.S. Cl.: 514/2, 12, 21

II. FIELDS SEARCHED

Minimum Documentation Searched *

Classification System	Classification Symbols
U.S. Cl.	514/2, 12, 21

Documentation Searched other than Minimum Documentation
to the extent that such documents are included in the fields searched *

APS, Medline, search terms: Alzheimer's disease, amyloid beta-protein,
administration or therapy

III. DOCUMENTS CONSIDERED TO BE RELEVANT *

Category *	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
<u>X</u> Y	US, A, 4,666,829 (Glenner et al) 19 May 1987. See Examples 1-12.	<u>6-11</u> 1-5
A	US, A, 4,816,416 (Averback) 28 March 1989. See entire document.	1-11
Y,P	US, A 4,912,206 (Goldgaber et al) 27 March 1990. See fig.3, columns 2-5.	1-11

* Special categories of cited documents: ¹⁰

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search

Date of Mailing of this International Search Report

19 May 1991

25 JUN 1991

International Searching Authority

Signature of Authorized Officer

ISA/IS

Richard Ekstrom
Richard Ekstrom